OMICS International
conferenceseries.com

Drug Des 2015, 4:2
http://dx.doi.org/10.4172/2169-0138.S1.008

International Conference and Expo on
Drug Discovery & Designing

August 11-13, 2015 Frankfurt, Germany

Toward full understanding of the EPR effect in primary and metastatic tumor, and issues of heterogeneity: For tumor selective delivery and imaging using nano-particles

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Tumor selective targeting using macromolecular drugs was started when poly (styrene-co-maleic acid) was conjugatedto protein (NCS) forming SMANCS in 1979.We then investigated most biocompatible plasma proteins,andsynthetic polymers of various sizesfor tumor uptake:We found >40KDa-polymers were selectively taken up into the tumor: This tumor selective uptakephenomenonwas coined EPR (enhanced permeability and retention)effect of solid tumors in 1986: The EPR reflectsarchitectural defect of tumor vasculature and excessive production of many vascular effectors as in inflammation, eg. bradykinin, nitric oxide, etc. EPR effect was also demonstratedin metastatic cancersrecently. Heterogeneity of EPR in many tumors may be caused by tumor thrombus or suppressed blood-flow. We showed several vascular mediators can augment EPR effect such as NO releasing agents and ACE-inhibitor (eg. enalapril) which potentiatesbradykinin.They not only restore vascular flow but also augment EPR effect for macromolecular delivery 2-3 folds. EPR effect will be similarly applied for delivery of fluorescent nanoprobes;it becomes beneficial for novelimaging and photodynamic therapy. Iv injection of fluorescent Zn-protoporphyrinnanoprobes in rat withautochthonous breast cancer, followed by 2-3 times photo-irradiation by endoscope, resultedin complete tumor regression. This advantage is also great value for in vivo tumor detection using fluorescent endoscope.

The EPR effect is yetthe first step for selective tumor delivery. However, drug translocation to tumor cell-membrane and intracellular target are remaining issues. We will show our state-of-the-art-for these points, utilizing tissue-pH of tumor (acidic), and membrane transportersupregulated in tumors.

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Lipophilic phenoxazines as potent and specific inhibitors of Akt signaling in rhabdomyosarcoma cells

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Phenoxazines shut down the activation of Akt/mTOR/p70S6/S6 kinase pathway and induce apoptosis to a considerable extent at about 100 nM level in rhabdomyosarcoma cells. Compounds having propyl bridge were less potent than compounds with 4 carbon chain length. This prompted us to continue the work by increasing the alkyl chain length to (-CH2)5 or (-CH2)6 at N10-position, hoping that the potency will be increased to a significant extent. Towards this goal, twenty one phenoxazines have been synthesized, characterized and examined for their ability to block the phosphorylation of Akt at serine 473 in cells. Serum starved Rh1 cells were exposed to 100 nM, 500 nM or 2000 nM phenoxazine derivatives for 4 h before stimulating with IGF-I (10 ng/m) for 10 min. Akt or Erk-1/2 phosphorylation was detected using the phospho-specific anti-Akt antibody or anti-Erk-1/2 antibody. The results demonstrate that out of 21 phenoxaznes tested, 10-[6'-[N-Diethyl] hexyl]-2-chlorophenoxazine (10D) and 10-[6'-[N-(β-Hydroxyethyl)-piperazino] hexyl]-2-chlorophenoxazine (15D) at 100 nM inhibited the phosphorylation of Akt at Ser 473 without affecting the phosphorylation of Erk-1/2. As we anticipated, the potency of the hexyl derivatives to inhibit the phosphorylation of Akt has been increased to a significant extent. 10D or 15D did not inhibit the activity of PDK1 or SGK1 but potently inhibited the kinase activity of recombinant Akt and Akt□PH. Further, 10D or 15D blocked IGF-I stimulated nuclear translocation of Akt in Rh1 cells and suppressed growth of Rh1, Rh18, and Rh30 cells (IC50 ≈ 100 nM) under serum-containing culture conditions at concentrations of agent consistent with Akt inhibition. Modeling studies suggest phenoxazines may bind in the ATP-binding site.

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